Becton Dickinson and Company
One Becton Drive
Mail Code 440
Franklin Lakes, NJ 07417-1880
(201) 847-7197
Fax (201) 847-7040
Aileen_Gilbert@BD.com

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Food and Drug Administration
Docket Management Branch (HFA-305)
5630 Fishers Lane Room 1061
Rockville, MD 20852

SUBJECT: Regulation Docket Number 99N-0193
Guidance: Docket Number 99D-0529

Attached is a hard copy of the Submission of Testimony given by Dr. Michael Gross. These documents have already been sent via E-Mail on 9/13/99. This serves as backup documentation.

Sincerely,

A. Gilbert

Aileen Gilbert
Regulatory Affairs
BD Pharmaceutical Systems

99D-0529

TS 2

ORAL PRESENTATION BY MICHAEL GROSS, PH.D., DIRECTOR CORPORATE REGULATORY AFFAIRS BECTON DICKINSON AND COMPANY CONCERNING THE PROPOSED RULE CONCERNING SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION (21CFR314.70) AND GUIDANCE FOR INDUSTRY, CHANGES TO AN APPROVED NDA OR ANDA

We wish to thank the Center for Drug Evaluation and Research for the opportunity to make a presentation at this public meeting. I will read my comments into the record and will submit a copy to the docket. They specifically concern the application of 21CFR 314.70 to drug and biological products packaged prefilled drug delivery devices. These prefilled drug-device combination products are most often regulated by CDER or CBER under a single application such as an NDA.

Becton Dickinson & Company, BD, is a manufacturer of medical and diagnostic systems. Our Pharmaceutical Systems Division manufactures functional pharmaceutical packaging systems for the pharmaceutical industry, for example Hypak prefillable glass syringe components and Sterifill prefillable plastic syringe components. BD also holds NDAs for device like products regulated under drug authorities and we currently hold several open INDs, some of which are for drug-device combination products.

In 1991 FDA published Product Jurisdiction regulations for combination products. Although combination products had been around for a long time, this was a formal recognition in regulation that combination products represent a special and potentially problematic case which was in needed of regulatory clarification. The Final Rule clarified which Center regulates a

specific combination product and under which authorities and regulatory mechanisms. Previously and still today, consistent with these regulations and Intercenter Agreements, drugs and/or biologics which are prefilled into functional packaging systems (device-like delivery systems such as prefilled syringes) may be regulated as drugs or biologics under a single application, an NDA, ANDA, PLA or BLA. But regardless of how they are registered, these products remain in fact combination products. Many pharmaceutical products are sold today in prefilled syringes and other delivery devices such as pens, autoinjectors, and inhalers.

The combination product issue extends beyond functional packaging systems to containers as simple as pharmaceutical vials. A year or two ago in an attempt to extend the labeling rule for medical devices containing latex, FDA suggested in a proposed rule a that pharmaceutical vials can be considered to

be the device component of a drug-device combination product. The extension of latex labeling rules to pharmaceutical products was ultimately stayed. Nonetheless, in the proposal, FDA conveyed the idea that pharmaceutical vials may be regulated as a device aspect of a drug-device combination product.

When regulations and guidance are being developed that will be applied to drug-device combination products which are prefilled functional drug dosage forms regulated under a single application CDER and CBER should not loose sight of the fact that these products are composed of drug and device aspects and not simply apply drug or biologic approaches in regulations to the device-like components of these systems. FDA should apply drug and biological product regulatory approaches to the drug and biological product aspects of these combination products and apply device regulatory requirements to the device-like aspects of these combination products. I am suggesting that

when 21CFR314.70 is published as a Final Rule, that the rule clearly address how changes in the manufacture of pharmaceutical packaging and pharmaceutical packaging components are to be handled. The current Rule and the proposed Rule and Guidance address this issue incompletely and frequently packaging and packaging component manufacturers are left to try to interpolate the regulation as it applies to packaging. The following slides, which I will submit in hard copy to the docket, provide distilled excerpts of the current regulations and new proposals to show how they addresses the reporting of changes for drug products and where it can become unclear to manufacturers and reviewers as to whether or not the rule in intended or should be applied to manufacturing changes in packaging and packaging components. These slides summarize packaging information to be submitted in prior approval and changes bein0g effected supplements and annual reports. Where the requirement or

guidance is clear, it is marked with a star. Where it is ambiguous it is marked with a bullet.

Because Chemistry-Manufacture and Controls information for packaging is often provided in Type III Drug Master Files which may be cross-referenced into hundreds of separate applications, the reporting and implementation of a change in the manufacture of pharmaceutical packaging and packaging components can become a coordination nightmare for sponsors and reviewers. Clearly identifying the possible changes that can occur in the manufacture of packaging and packaging components and specifically addressing how these changes are to be reported would help packaging manufacturers understand how their customers are to report changes that packaging manufacturers may make and thus how these manufacturers must report these changes to their customers. These rules should be provided in the new Final Rule and Guidance. Or, if not then

they should be addressed in separate guidance.

The second point I would like to make concerns the use of packaging equivalence protocols, which are codified in the current Final Rule and the proposed Rule and in a sense represent a subset of comparability protocols. We recommend that FDA encourage the use packaging equivalency protocols to reduce regulatory reporting burdens, expedite approvals of manufacturing changes and simplify reporting coordination for packaging manufacturers. Based on personal experience and input from others in the industry, while packaging equivalence protocols are allowed by regulation, their use may be discouraged by reviewers. It has recently been suggested to me that my plan to include a packaging equivalency protocol in an NDA was not a good idea and would complicate and potentially

delay the review of an NDA. It was suggested that the protocol be submitted after initial approval as a supplemental application. I believe that such prospective agreements about how the effects of packaging manufacturing change are to be assessed and reported are beneficial to both FDA and industry. They reduce unpredictability and establish prospective agreements that can be relied upon for the life on an application. I would also like to suggest that such protocols may be submitted within Type III Drug Master Files in order to expedite the implementation of manufacturing change at the packaging and packaging component manufacturer level.

In summary, we would ask FDA to specifically address in the Final Rule and/or Guidance or in separate Guidance how changes in the device aspect of a drug-device combination product is to be reported in applications. When establishing rules for reporting changes in packaging and packaging

components, FDA should not simply apply the rules for changes to drugs/biologics to the device-like aspects of combination products. Rather, FDA should consider how the equivalent change is managed for the analogous medical device and apply this kind of approach. Finally, if new parts of this proposed rule and guidance are developed to address these issues, the industry should have another opportunity to provide specific input and comment on these additions.

CURRENT 314.70: DRUG PRODUCT

(b) PRIOR APPROVAL SUPPLEMENT

- **add or delete an ingredient, change the composition**
- **change the method of manufacture; changing/relax in-process control;**
- **use different facility/establishment/contract laboratory, to manufacture, process, or package**
- **relax specification**
- ★ **change container/closure system material; change a specification/regulatory analytical method for the container and closure system**

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CURRENT 314.70: DRUG PRODUCT

(d) ANNUAL REPORT

- ★ **change to the container/closure system, except a change in container size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.**
- **addition or deletion of an alternate analytical method.**

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PROPOSED 314.70: DRUG PRODUCT

PRIOR APPROVAL SUPPLEMENT

- **Change in the qualitative or quantitative formulation or specifications including inactive ingredients**
- **Change that may affect product sterility assurance, such as changes in product or component sterilization method(s)**
- ★ **Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product**

CBE-30 SUPPLEMENT

- ★ **Change in container closure system not affecting quality of drug product**

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PROPOSED 314.70: DRUG PRODUCT

CBE SUPPLEMENT

- **Addition to a specification change, methods/controls providing increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency**

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PROPOSED 314.70: DRUG PRODUCT

Annual Report

- **Replacement of equipment of the same design/operating principles**
- ★ **Change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.**

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DRAFT GUIDANCE

Prior Approval Supplement

- ★ **Manufacturing change that may affect the release/metering/ other characteristics of the dose delivered**
- **Change that may affect product sterility assurance**
  - **Changes in the sterilization method(s)**
  - **Changes in sterilizer load configurations that are outside the range of preciously validated loads**
- ★ **Change in primary packaging involving new plastics or rubbers, inks, adhesives not previously approved by CDER for use with the particular liquid dosage form**
- ★ **Change in the primary packaging component controlling dose delivered/bioavailability**

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DRAFT GUIDANCE

Annual Report

- ★ **Change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application and the facility has a satisfactory CGMP inspection for the type of operation being performed.**
- ★ **Change in container closure system for a non-sterile drug product, based upon showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium**

HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CROSS REFERENCE SHEET

Docket Number/Item Code:	99N-0193/TS2
See Docket Number/Item Code:	99D-0529/TS2

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